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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,744	03/25/2005	Noboru Maki	053466-0395	7902

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EXAMINER	
PENG, BO	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/526,744	**Applicant(s)** MAKI ET AL.	
	Examiner BO PENG	**Art Unit** 1648	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 22 December 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *5* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *1/16/09*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *The amendment to Claim 6 raises a new issue: A new rejection of Claim 6 under 103 would have been made on the same ground as that of the outstanding 103 rejection of Claims 1-4.*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-6 and 21*.
   Claim(s) withdrawn from consideration: *7-20*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/BO PENG/
Examiner, Art Unit: 1648

Continuation of 11. does NOT place the application in condition for allowance because:

(Prior rejection-maintained) The rejection of Claim 4 under 112, 1st paragraph, for failing to comply with written description requirement, is maintained for the reason of record.
Applicant again argues that Sakamoto et al. shows on p. 681 that "there are many particles containing DNA which are HBV-like particles and yet not HBV core particles". Applicant also argues that the specification in Fig. 3 and 4 discloses HBV particles formed from precore protein.
These arguments have been found not persuasive. The claim requires "...HBV-like particles contains precore protein of Claim 1, further not comprising HBV DNA therein". Thus, "many particles containing DNA which are HBV-like particles and yet not HBV core particles", shown in Sakamoto et al., do not support the description of the claimed "HBV-like particles contains precore protein of Claim 1, further not comprising HBV DNA therein". Other reasons have been discussed in the previous Office action, see e.g. Para 11, the Final Office action dated July 21, 2008.
Fig. 3 and 4 of the specification do not teach any HBV-like particles that meet the claim limitation, either. It is noted that Fig. 3 and 4 show four constructs: (1) HBcrAg, (2) HBcAg, (3) HBV-DNA, and (4) HBsAg protein. None of them meet the structural limitation of "HBV-like particle comprising an isolated HBV precore protein of Claim 1, further not comprising HBV DNA therein". Specifically, HBcrAg (1) and HBcAg (2) are capable of forming core-like particles without DNA, but they are not HBV-like particles. HBV-DNA (3) apparently contains DNA. However, the claim requires the claimed HBV-like particle contain precore protein, but not contain DNA. Finally, HBsAg protein (4) is a protein. Thus, neither Fig. 3 nor Fig. 4 supports the Applicant's argument.
For the above reason, Applicant's arguments are not persuasive. The rejection is maintained.

(Prior rejection-maintained) The rejection of Claims 1 and 3-6 under 35 U.S.C. 112, first paragraph for failing to comply with the enablement requirement (scope of enablement), is maintained for the reasons of record.
Applicant argues that a person of ordinary skill in the art would be able to obtain these HBV particles formed from precore protein, which do not contain HBV core and DNA by the methods described in Example 3 and 4 of the specification.
However, based on the specification, Example 3 teaches analysis of HBe (precore product) by the western blot method, and Example 4 teaches analysis of the HBV core-related antigen amino acid sequence by MALDI mass spectrometry. Neither Example 3 nor 4 teach how to make and use HBV virus-like particles comprising the isolated HBV precore protein of Claim 1, further not comprising HBV DNA therein. Thus, Applicant's argument is not persuasive. The rejection is maintained.

(Prior rejection-maintained) The rejection of Claim 21 under 35 U.S.C. 102(b), as being anticipated by Takahashi (J. Immunology, 147(9): 3156-3160, 1991) is maintained for the reason of record.
Applicant argues that Claim 21 has been amended to describe a specific antibody. Takahashi does not describe a specific antibody. Therefore, Takahashi does not anticipate claim 21.
However, this argument is not relevant because it's based upon the amendment to the claim, which has not been entered into the application. The arguments are therefore not found persuasive with respect to the claims as presently pending in the application. The rejection is maintained for the same reasons as set forth in the previous Office action.

(Prior rejection-maintained)The rejection of Claims 1-4 under 35 U.S.C. 103(a) as being unpatentable over Takahashi (J. Immunology, 147(9):3156-3160, 1991, cited in IDS), in view of Kobayash, is maintained for the reasons of record.
Applicant argues that among four disclosed precore products comprising p21c, p20, pl8 and pl7 described by Takahashi, only one (p21c) has a particle form. However, p21c reacts with a monoclonal antibody (2212) which recognized the C-terminus (amino acids 150-183) of HBcAg. Applicant argues that the precore protein of the present invention does not react with antibody HB50 that recognizes the HBcAg C-terminus. Thus, the present precore protein and the p21c described in Takashi are different within their C-termini, and Takahashi does not teach or suggest the current invention.
This argument is not convincing. First, the instant Claims 1, 3 and 4 do not require the claimed precore protein lack of C-terminus (amino acids 150-183) of HBcAg. Thus this argument is not relevant to Claims 1, 3 and 4. Moreover, Takahashi teaches that precore products p20e, p18e and p17e do not bind with mAb against the C-terminal domain of the full length HBc. Precore product p17e has its C-terminus at amino acid 149, see e.g. Discussion p. 3158. Thus, Takahashi teaches precore proteins that lacks C-terminus (amino acids 150-183) of HBcAg. Thus, Applicant's argument based on "the C-terminal domain" is not persuasive.
Secondly, Applicant argues limitations that are not in the claims. The claims are not drawn to a HBV procure particle, but are drawn to an HBV precore protein that has the ability to form core-like particles of HBV and which contain all or part of the signal sequence comprising amino acids at positions -29 to -11 (Emphasis added). As indicated in the previous Office action dated December 14, 2007, Kobayashi teaches the HBV precore protein (subtype adr), which comprises an amino acid sequence 99.6% identical to the instant SEQ ID NO: 1, and which contains all or part of the signal sequence at positions -29 to -11, as evidenced by sequence alignment. Furthermore, Takahashi teaches the HBV precore (subtype adr) forms multiple products: p21c, p20e, p18e and p17e, which have the same coding sequences, but have different N-terminal signal sequences, wherein precore product p21c forms particles. Thus, the combined teaching of Kobayashi and Takahashi indicates that HBV precore proteins (subtype adr) of prior art has the ability to form core-like particles of HBV, contain all or part of the signal sequence at position -29 to -11, and have either full length (amino acids 150-183 of HBcAg) or a C-terminus at amino acid 149 as set forth in SEQ ID NO: 1. Thus, the precore proteins of the prior art have substantially same structures and properties as the claimed HBV precore proteins.
Finally, it is noted that this is an obviousness type rejection. Thus, the cited references need not match the precise sequence of the present claims if they represent obvious variations of the claimed precore proteins. As indicated in the previous office actions, the claimed precore protein appears to be an obvious variation of the precore protein in the prior art.
"[W]hen one steps back and views the twisted structure of the protein as a whole, and considers the overall similarity of the protein of the prior art versus that coded for by the DNA claimed herein, and also considers the similarity of the DNA of the prior art versus that claimed herein, the minor change in the chemical configuration or design of the molecule discovered or made by appellants is so negligible that a

prima facie case of obviousness exists. In legal parlance, on the record herein appellants' structural modification is de minimis." Ex parte Anderson, 30 USPQ2d 1866

In the present case, specifically, the precore protein of HBV adr subtype, disclosed by Kobayashi, differs from the claimed HBV precore protein comprising SEQ ID NO: 1 of Claim 3 by only one amino acid, V119T, in the coding region. However, it is known in the art that different HBV strains of same subtype can have some amino acid variations. One amino acid difference (in this example V119T) apparently does not affect the ability of the precore protein to form core-like particles, as shown by Takahashi. Because the claimed precore proteins encompass full length and processed HBV precore proteins, which have structures and properties equivalent to the precore proteins of HBV adr subtype as taught by Takahashi and Kobayashi, they are obvious variations of the prior art precore protein. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. The rejection is maintained.